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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,773	01/27/2004	Gregory J. LaRosa	1855.1052-028	3246

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EXAMINER	
BOESEN, AGNIESZKA	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,773	LAROSA ET AL.	
	Examiner	Art Unit	
	Agnieszka Boesen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-52,54,55,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-52,54,55,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed May 18, 2007 in response to the Office Action of October 13, 2006 is acknowledged and has been entered. Claims 36, 49, 52 and 54 have been amended. Claims 53 and 56 have been canceled. Claims 36-52, 54, 55, 57 and 58 are pending and under examination.

Double Patenting Rejection

Rejection of claims 36, 37, 49, 50, 51, 54, and 56-58 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 7, 8, and 41-43 of U.S. Patent No. 6,312,689 B1 in view of Owens et al. (Journal of Immunological Methods, 1994) **is withdrawn** in view of Applicants' submission of a Terminal Disclaimer under 37 C.F.R. §§ 3.73(b) and 1.321(b).

Rejection of claims 36-48, and 52 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-72 of U.S. Patent No. 6,352,832 B1 **is withdrawn** in view of Applicants' submission of a Terminal Disclaimer under 37 C.F.R. §§ 3.73(b) and 1.321(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 36 and 53 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement **is withdrawn/moot** in view of Applicants' amendment and cancellation of claim 53.

New Rejection

Claims 36-52, 54, 55, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Claims are drawn to a method of treating a CCR2-mediated disorder in a patient comprising administering to the patient an effective amount of a humanized immunoglobulin or antigen-binding fragment thereof having binding specificity for CCR2. The humanized immunoglobulin comprises a heavy chain and a light chain, wherein said light chain comprises at least one complementarity determining region (CDR) derived from murine monoclonal antibody 1D9 and a framework region derived from the light chain of human antibody HF-21/28, and wherein said heavy chain comprises at least one complementarity determining region derived

from murine monoclonal antibody 1D9 and a framework region derived from the heavy chain of human antibody 4B4'CL.

The claims are rejected because the present disclosure is not commensurate with the scope of the claims. The skilled artisan would be unable to practice the current method in the broad scope as claimed, because the present claims encompass using humanized antibodies comprising partial antigen binding regions that are insufficient to confer binding specificity for CCR2. The present claims do not require that the humanized immunoglobulin used in the current method must comprise a complete antigen binding region, which typically consists of six complementarity determining regions or a complete variable heavy and variable light chain. Additionally, the antibodies of the present method encompass undefined derivatives. The skilled artisan would be unable to practice the present method using humanized immunoglobulin comprising a heavy chain and a light chain, wherein said light chain comprises **at least one complementarity determining region (CDR) derived** from murine monoclonal antibody 1D9 and a framework region derived from the light chain of human antibody HF-21/28, and wherein said heavy chain **comprises at least one complementarity determining region derived** from murine monoclonal antibody 1D9 and a framework region derived from the heavy chain of human antibody 4B4'CL.

The specification discloses that the antigen binding region of the humanized immunoglobulin of the present invention comprises **three CDRs** derived from the light chain of the 1D9 antibody, and the heavy chain comprises **three CDRs** derived from the heavy chain of the 1D9 antibody. The specification also discloses that a humanized light chain comprises the **variable region of the light chain** shown in FIG. 7 (SEQ ID NO: 9), and a humanized heavy

chain comprises the **variable region of the heavy chain** shown in FIG. 8 (SEQ ID NO: 10) (see below). Thus in order for an antibody to bind antigen, an antibody must comprise a variable region of the light chain comprising three CDRs and variable region of the heavy chain comprising three CDRs.

It is noted that the specification does not define the term "derived" and thus under broadest reasonable interpretation the term "derived" encompasses antibody and CDR fragments that originate from any part of the 1D9 antibody.

[0009] "For example, the humanized immunoglobulin or antigen-binding fragment thereof can comprise an antigen binding region comprising at least one complementarity determining region (CDR) of nonhuman origin, and a framework region (FR) derived from a human framework region. In one aspect, the humanized immunoglobulin having binding specificity for CCR2 comprises a light chain comprising at least one CDR derived from an antibody of nonhuman origin which binds CCR2 and a FR derived from a light chain of human origin (e.g., from HF-21/28), and a heavy chain comprising a CDR derived from an antibody of nonhuman origin which binds CCR2 and a FR derived from a heavy chain of human origin (e.g., from 4B4'CL). In another aspect, the light chain comprises three CDRs derived from the light chain of the 1D9 antibody, and the heavy chain comprises three CDRs derived from the heavy chain of the 1D9 antibody."

[0010] "The present invention also relates to humanized immunoglobulin light chains and antigen-binding fragments thereof (e.g., comprising CDR1, CDR2 and CDR3 of the light chain of the 1D9 antibody, and a human light chain FR), and to humanized immunoglobulin heavy chains and antigen-binding fragments thereof (e.g., comprising CDR1, CDR2 and CDR3 of the heavy chain of the 1D9 antibody, and a human heavy chain FR). In a preferred embodiment, the invention relates to humanized heavy and light chains described herein (e.g., a humanized light chain comprising the variable region of the light chain shown in FIG. 7 (SEQ ID NO: 9), a humanized heavy chain comprising the variable region of the heavy chain shown in FIG. 8 (SEQ ID NO: 10)."

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and

conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Single amino acid substitution altering antigen-binding specificity. PNAS, 1982, Vol 79, p. 1979-1983). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Panka et al. (Variable region framework differences result in decreased or increased affinity of variant anti-digoxin antibodies, PNAS, 1988, Vol. 85, p. 3080-3084) demonstrate that a single amino acid substiution of serine for alanine results in decreased affinity. Li et al. (Three-dimentional structures of the free and antigen-bound Fab from monoclonal antilysozyme antibody HyHEL-63, Biochemistry, 2000, Vol. 39, p. 6296-6309) in a study of three-dimensional structures of an antigen-bound Fab fragment of a monoclonal antibody, disclose that all six CDRs of the Fab variable domains are involved in binding the antigen (see entire document, particularly page 6301).

Thus the state of the art recognizes that an antibody with antigen binding specificity must necessarily comprise all three CDRs of the heavy chain variable region and all three CDRs of the light chain variable region. As discussed above, the present claims do not require that all three CDRs of both heavy and light chain of 1D9 antibody are present within the antibody of the

present invention. Furthermore, the structure of an antibody claimed to have particular antigen specificity should be precisely defined as described in the present specification, which provides sequences representing particular variable heavy and light chains (see [0009] and [0010]). However because the claims encompass partial CDR structures in form of derivatives, the claims are not commensurate with the enabling disclosure. A CDR derivative of the 1D9 antibody may comprise just the partial structure of the CDR region within the 1D9 antibody. One of skill in the art would neither expect nor predict that an antibody comprising partial CDR structure(s) would have the functionality to bind an antigen of interest.

Considering the complexity of the diseases such as restenosis, multiple sclerosis or rheumatoid arthritis aimed to be treated in the presently claimed method, it is highly unpredictable that the skilled artisan would be able to treat the said diseases by administering antibodies that may or may not have binding affinity to CCR2 molecule.

As noted above the present claims are broader than the enabling disclosure. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Therefore considering the knowledge in the art with regard to the structure of the antibody antigen binding region, and the unpredictable changes in antibody binding affinity resulting from minor alterations in the CDR regions, it is apparent that the ordinary artisan would be unable to practice the present invention to the full extend as claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on Monday – Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AB

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